1521-0081/12/6403-621–644$25.00
PHARMACOLOGICAL REVIEWS
Vol. 64, No. 3
4952/3772316

Pharmacol Rev 64:621–644, 2012

ASSOCIATE EDITOR: ULF SIMONSEN

Pharmacology for the Treatment of Premature Ejaculation

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This article is available online at http://pharmrev.aspetjournals.org.
http://dx.doi.org/10.1124/pr.111.004952.

***Abstract*——Male sexual response comprises four phases: excitement, including erection; plateau; ejaculation, usually accompanied by orgasm; and resolution. Ejaculation is a complex sexual response involving a sequential process consisting of two phases: emission and expulsion. Ejaculation, which is basically a spinal reflex, requires a tight coordination between sympathetic, parasympathetic, and somatic efferent pathways originating from different segments and area in the spinal cord and innervating pelvi-perineal anatomical structures. A major relaying and synchronizing role is played by a group of lumbar neurons described as the spinal generator of ejaculation. Excitatory and inhibitory influences from sensory genital and cerebral stimuli are integrated and processed in the spinal cord. Premature ejaculation (PE) can be defined by ≤1-min ejaculatory latency, an inability to delay ejaculation, and negative personal consequences. Because there is no physiological impairment in PE, any pharmacological agent with central or peripheral mechanism of action that is delaying the ejaculation is a drug candidate for the treatment of PE. Ejaculation is centrally mediated by a variety of neurotransmitter systems, involving especially serotonin and serotonergic pathways but also dopaminergic and oxytocinergic systems. Pharmacological delay of ejaculation can be achieved either by inhibiting excitatory or reinforcing inhibitory pathways from the brain or the periphery to the spinal cord. PE can be treated with long-term use of selective serotonin-reuptake inhibitors (SSRIs) or tricyclic antidepressants. Dapoxetine, a short-acting SSRI, is the first treatment registered for the on-demand treatment of PE. Anesthetics applied on the glans penis have the ability to lengthen the time to ejaculation. Targeting oxytocinergic, neurokinin-1, dopaminergic, and opioid receptors represent future avenues to delaying ejaculation.**

I. Introduction

The male sexual cycle has been divided into four successive stages (Masters and Johnson, 1966; Kaplan, 1979): desire, excitation, orgasm, and resolution, with ejaculation being the culmination of male sexual behavior and intimately associated with orgasm, which represents the most reinforcing component of sexual behavior. Ejaculation can be defined as forceful propulsion out of the body, through the urethral meatus, of sperm, which is composed of the male reproductive cells (spermatozoa) in suspension in a protective and nutritive milieu (seminal fluid). Ejaculation consists of the synchronized succession of physiological events that form two distinct phases: emission and expulsion. Emission corresponds to the secretion of the different components of sperm from accessory sex glands and testes into the urethra. Expulsion is the intense and rhythmic contractions of pelvi-perineal striated muscles that lead to the emptying of sperm from the urethra.

Ejaculatory disorders, which can alter one or two phases of ejaculation, include heterogeneous dysfunctions with a variety of organic, psychogenic, and/or iatrogenic etiologies. Some of those dysfunctions, such as anejaculation (i.e., complete inability to ejaculate) and retrograde ejaculation (i.e., sperm propelled backward

into the bladder through uncontracted bladder neck), are causes of infertility. Others, such as premature and delayed ejaculation, usually do not result in fertilization challenge. However, because of its prevalence and possible considerable impact on the quality of life of men and couples, premature ejaculation (PE[1]) is a major concern in sexual medicine. Indeed, both men and their partners affirm negative effects and interpersonal difficulty related to PE and an overall reduction in their quality of life (Althof et al., 2010). Variability of ejaculatory time is a common situation among men (Waldinger and Schweitzer, 2006a,b). However, the delay for ejaculation to occur can be repeatedly short.

In the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2000), PE is defined as a "persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it." PE can only be diagnosed when "the disturbance causes marked distress or interpersonal difficulty." According to the *International Statistical Classification of Diseases and Related Health Problems* (World Health Organization, 1994) endorsed by the 43rd World Health Assembly in May 1990 and used in WHO Member States since 1994, PE is defined as "the inability to delay ejaculation sufficiently to enjoy lovemaking, which is manifested by either an occurrence of ejaculation before or very soon after the beginning of intercourse (if a time limit is required: before or within 15 seconds of the beginning of intercourse) or ejaculation occurs in the absence of sufficient erection to make intercourse possible." More recently the International Society for Sexual Medicine (ISSM) created a contemporary, comprehensive, evidence-based definition of PE (McMahon et al., 2008). It was agreed that the constructs that are necessary to define premature ejaculation are as follows: time to ejaculation, inability to delay ejaculation, and negative consequences from PE. Accordingly, PE has been defined as a male sexual dysfunction characterized by "ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, and inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy."

PE has long been a privileged field for psychiatrists and psychologists, behavioral and psychological procedures being the only treatment options proposed. However, on the basis of seminal works by Schapiro (1943) and Eaton (1973) and subsequent clinical observations (meta-analysis by Waldinger, 2003), a neurobiological concept of PE has emerged. This eventually led to the development of the first prescription drug (dapoxetine) registered specifically for the on-demand treatment of PE.

In the first part, a comprehensive background of the neurophysiology and neuropharmacology of ejaculation is provided. Thereafter, a description of PE and its current pharmacological treatments is presented followed by potential advances in this field.

II. Neurophysiology of Ejaculation

A. Peripheral Regulation

Organs and anatomical structures of the urogenital tract involved in ejaculation can be divided in two categories depending on the phase in which they participate. Those that take part in emission include 1) seminal vesicles, prostate, and bulbourethral glands, which produce ~99% of the seminal fluid and 2) vas or ductus deferens, which conducts spermatozoa from epididymis to urethra. Components that participate to expulsion include 1) pelvi-perineal striated muscles, with a major role for the bulbospongiosus muscle, which rhythmically contracts to powerfully propel sperm through the urethra, and 2) bladder neck sphincter, which intensely contracts to prevent sperm from flowing backward into the bladder (retrograde ejaculation). Coordinated activation of the anatomical elements guarantees a correct ejaculatory response.

1. Sensory Receptors and Afferent Pathways. The dorsal nerve of the penis, a sensory branch of the somatic pudendal nerve, is the main sensory afferent involved in ejaculation. The dorsal nerve of the penis conveys inputs from sensory receptors located in the penile skin, prepuce, and glans toward the upper sacral and lower lumbar segments (in rodents) of the spinal cord (Núñez et al., 1986; Johnson and Halata, 1991). Most of the sensory terminals located in the glans are made of free nerve endings but there also encapsulated receptors, namely Krause-Finger corpuscles (Halata and Munger, 1986). Those receptors, activated by low-frequency vibrations, are the neurobiological substrate for the starting point of the ejaculatory reflex elicited by mechanical stimulation of the glans penis. In addition, sensory signals from various peripheral areas, such as penile shaft, perineum, and testes, can cumulate with excitatory inputs originating in Krause-Finger corpuscles. In different mammalian species, a relatively sparse sensory innervation of vas deferens, prostate gland, and

[1]Abbreviations: α-MSH, α-melanocyte stimulating hormone; 5-HT, 5-hydroxytryptamine (serotonin); CCK-8, cholecystokinin octapeptide fragment; CNS, central nervous system; crSSRI, chronic selective serotonin reuptake inhibitors; GRP, gastrin-releasing peptide; IELT, intravaginal ejaculation latency time; ISSM, International Society for Sexual Medicine; LH, lateral hypothalamus; LSt, lumbar spinothalamic; MPOA, medial preoptic area; NK1, neurokinin-1 receptor; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; nPGi, paragigantocellular nucleus; ODT, orally disintegrating tablet; OH-DPAT, hydroxy-2-dipropylaminotetralin; OT, oxytocin; P2, purinergic-2; PCA, *p*-chloroamphetamine; PDE, phosphodiesterase; PE, premature ejaculation; PET, positron emission tomography; PVN, paraventricular hypothalamic nucleus; SGE, spinal generator for ejaculation; SP, substance P; SPFp, subparafascicular thalamus, parvicellular part; SSRI, selective serotonin-reuptake inhibitor; TIP39, tuberoinfundibular peptide 39.

urethra has been described that reaches the spinal cord via the pudendal nerve (Pennefather et al., 2000; Kaleczyc et al., 2002). The hypogastric nerve contains another set of afferent fibers that, after passing through the paravertebral sympathetic chain, enter the spinal cord via posterior thoracolumbar dorsal roots (Baron and Jänig, 1991). The cell bodies of primary sensory neurons innervating peripheral anatomical structures participating in ejaculation are located in lumbar dorsal root ganglia, and their central projections terminate in the medial dorsal horn and the dorsal gray commissure of the corresponding spinal cord segments (McKenna and Nadelhaft, 1986; Ueyama et al., 1987). Sensory inputs have been shown sufficient to elicit expulsion reflex (i.e., coherent activation of pelvi-perineal muscles) or even complete ejaculatory response (i.e., forceful expulsion of semen) in laboratory animals and humans after complete spinal cord lesion (Nordling et al., 1979; McKenna et al., 1991; Brackett et al., 1998; Johnson and Hubscher, 1998).

2. Efferent Pathways and Final Output. All the pelvic components contributing to ejaculation receive specific autonomic (both sympathetic and parasympathetic for most of them) or somatic efferent innervation.

a. Sympathetic innervation. After exiting the spinal column via ventral roots, a bunch of sympathetic fibers relay in the paravertebral sympathetic chain and then proceed via the splanchnic nerves to the inferior mesenteric ganglia or superior hypogastric plexus (Owman and Stjernquist, 1988). Another set of fibers travels in the paravertebral chain, relays in the celiac superior mesenteric ganglia, and then reaches the inferior mesenteric ganglia via the intermesenteric nerves (Owman and Stjernquist, 1988). From these ganglia emanates the hypogastric nerve, which joins the parasympathetic pelvic nerve to form the pelvic or inferior hypogastric plexus.

b. Parasympathetic innervation. Axons of the preganglionic parasympathetic neurons travel throughout the pelvic nerve and synapse with postganglionic cells lying in the pelvic plexus. From the pelvic plexus arise nerves conveying sympathetic and parasympathetic outflow to epididymis, vas deferens, seminal vesicle, prostate, bladder neck, and urethra.

Both sympathetic and parasympathetic tones act in a synergistic fashion to initiate seminal emission by activating epithelial secretion and smooth muscle contraction throughout the seminal tract. In various mammals, including humans, semen can be obtained by stimulation of the sympathetic and parasympathetic nerves destined for ejaculatory tissues (Watanabe et al., 1988; Brindley et al., 1989; Kolbeck and Steers, 1992; Kontani and Shiraoya, 2002). Traumatic or postsurgical disruption of sympathetic pathways innervating the seminal tract is a cause of ejaculatory dysfunction (anejaculation or retrograde ejaculation) in men (May et al., 1969; Pocard et al., 2002).

c. Somatic innervation. Somatic fibers convey motor outputs, via the motor branch of the pudendal nerve, to the pelvi-perineal striated muscles, including bulbospongiosus, ischiocavernosus, and levator ani muscles as well as external urethral sphincter (Schrøder, 1985). Motor outputs are responsible for characteristic synchronized intense and rhythmic contractions of relevant muscular elements, which explains the pulsatile ejection of sperm at the urethral meatus (Gerstenberg et al., 1990). Concomitant with striated muscle contractions is the orgasmic feeling or climax accompanying ejaculation. Trauma or neuropathy affecting the pudendal nerve prevents the expulsion phase from occurring, thus leading to ejaculatory dysfunctions such as retrograde or dribbling ejaculation (Grossiord et al., 1978; Vinik et al., 2003).

B. Spinal Cord Regulation

1. Autonomic and Somatic Centers. Soma of the preganglionic sympathetic neurons are located at the level of the lower thoracic and upper lumbar segments of the spinal cord in the intermediolateral cell column and in the central autonomic region (Morgan et al., 1986; Nadelhaft and McKenna, 1987) in rats. The sacral parasympathetic nucleus, which corresponds to the intermediolateral cell column of the upper sacral segments (in humans) and lumbosacral segments (in rodents) of the spinal cord, contains the cell bodies of preganglionic parasympathetic neurons (Nadelhaft and Booth, 1984). Soma of the motoneurons commanding the pelvi-perineal muscles responsible for the expulsion phase, lie in the Onuf's nucleus located in the ventral horn of the upper sacral spinal segments in humans and lumbosacral spinal segments in rodents.

The autonomic and somatic spinal ejaculatory nuclei play a pivotal role in ejaculation as they integrate peripheral and central signals and send coordinated outputs to ejaculatory tissues (Fig. 1). Coordination of autonomic and somatic final commands is achieved by a spinal generator identified in the male rat (Truitt and Coolen, 2002).

2. Spinal Generator for Ejaculation. The spinal generator for ejaculation (SGE) is composed of cells that reside around the central canal, in laminae X and VII (medial part) of the third and fourth spinal lumbar segments in rats (Truitt and Coolen, 2002). Because these cells were also previously known as projecting to the parvicellular division of the subparafascicular nucleus of the thalamus, they are referred to as lumbar spinothalamic (LSt) neurons (Ju et al., 1987). A great majority of LSt neurons contain galanin and cholecystokinin (Ju et al., 1987; Truitt et al., 2003), and express the preferential receptor for substance P (SP) neurokinin-1 receptor (NK1; Truitt and Coolen, 2002). In addition, numerous LSt neurons have been found to contain enkephalin and gastrin-releasing peptide (Nicholas et al., 1999; Sakamoto et al., 2008). Neuroanatomical tracing studies were

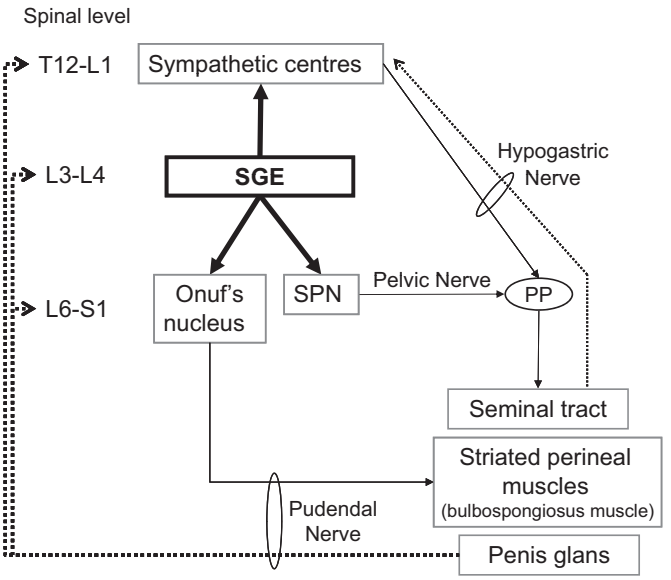

FIG. 1. Schematic view of the spinal network of ejaculation in the male rat. Solid lines symbolize efferent pathways. Dashed lines symbolize afferent pathways, and thickness represents the density of innervation. L, lumbar spinal segment; PP, pelvic plexus; S, sacral spinal segment; SPN, sacral parasympathetic nucleus; T, thoracic spinal segment.

performed to describe the spinal ejaculation circuitry. It was demonstrated that LSt neurons project to sympathetic and parasympathetic preganglionic neurons innervating the prostate and seminal vesicles (Xu et al., 2005; Sun et al., 2009). Moreover, connections between LSt and motor neurons of the dorsomedial nucleus innervating the bulbospongiosus muscles have been reported (Xu et al., 2005). It is noteworthy that most of the LSt neurons are probably in direct connection with both autonomic (sympathetic and/or parasympathetic) and somatic neurons (Xu et al., 2006). Functional investigations were undertaken to support the crucial role LSt neurons play in ejaculation. The selective lesion of this group of cells by targeting NK-1 receptors in male rats free to copulate resulted in abolition of ejaculation ability, whereas the other components of sexual behavior (motivation, erection, etc.) were not affected (Truitt and Coolen, 2002). Electrical microstimulation applied to anesthetized male rats in the spinal area where LSt neurons are located elicits ejaculation with motile spermatozoa detected in expelled sperm (Borgdorff et al., 2008). As a whole, the above experimental evidence supports a crucial role for LSt neurons in orchestrating secretory and motor commands leading to ejaculation.

It has moreover been postulated that LSt neurons may serve as a relay for ejaculation-related sensory stimuli from the periphery to the brain structures, where the orgasmic feeling raises. Fibers of the sensory branch of the pudendal nerve, which conveys sensory stimuli originating in the genital area, terminate close to LSt neurons (McKenna and Nadelhaft, 1986), although a direct connection remains to be demonstrated.

Despite recent decisive progress in our understanding of spinal command of ejaculation, some questions remain on SGE functioning. More notably, the abundance of projections and neuropeptides identified to date suggest that several subpopulations of neurons exist in the SGE area that are likely to have different roles in ejaculation (e.g., integration, synchronization, or relay). In addition, neuropeptides detected in LSt neurons are usually coreleased with conventional neurotransmitters for modulating neural transmission, but these conventional neurotransmitters have not yet been characterized.

Integrity of LSt and spinal autonomic and somatic centers is necessary and sufficient for the expression of ejaculation, as demonstrated in rats with spinal cord transection at the thoracic level (Yonezawa et al., 2000; Borgdorff et al., 2008) and in men with complete lesion of the spinal cord (Brackett et al., 1998). Nevertheless, a great body of evidence supports the existence of strong brain control over spinal mechanisms of ejaculation.

C. Brain Regulation

Delineating the exact role a brain area plays in ejaculation is complicated by the fact that ejaculation is strongly mingled with other sexual and behavioral responses (e.g., desire, motivation, erection, orgasm, and even social relationships). In addition, the ejaculatory response is a short-lasting phenomenon in the majority of mammalian species, with rapid CNS neurochemical changes. However, the use of certain techniques associated with adequate experimental paradigms permitted to identify groups of neurons specifically involved in ejaculation (Fig. 2). More notably, analysis of c-Fos protein expression pattern in behavioral studies led to the detection of neurons belonging to a brain circuitry specifically controlling ejaculation in rats and gerbils (Coolen et al., 1998; Heeb and Yahr, 2001; Hamson and Watson, 2004).

1. Sensory/Integrative Areas. Activated neurons related to ejaculation have been located in small regions lying within the posteromedial bed nucleus of stria terminalis, the posterodorsal medial amygdaloid nucleus, the posterodorsal preoptic nucleus, and the parvicellular

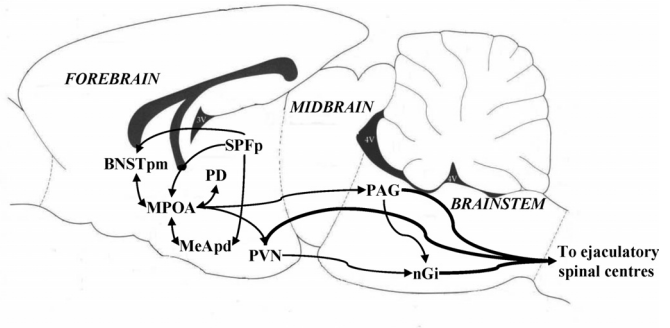

FIG. 2. Schematic view of the brain network of ejaculation in the male rat. BNSTpm, bed nucleus of the stria terminalis posteromedial; nGi, gigantocellular nucleus; MeApd, medial amygdala posterodorsal; PAG, periaqueductal gray; PD, posterodorsal preoptic.

part of the subparafascicular thalamus (SPFp). One limitation of c-Fos analysis resides in the fact that a causal relationship between neuronal activation and the examined neurophysiological response cannot be clearly established. However, several lines of neuroanatomical and functional evidence strongly suggest that the neurons exhibiting increased level of c-Fos exclusively during ejaculation are involved in the processing of sexually relevant information, including sexual cues and peripheral somatosensory stimuli (Baum and Everitt, 1992; Coolen et al., 1997; Heeb and Yahr, 2001).

2. Excitatory Areas. Reciprocal connections between the substructures listed above and the medial preoptic area (MPOA) of the hypothalamus, a brain area known as essential in controlling sexual behavior (Meisel and Sachs, 1994), has been reported in anatomical and functional studies (Coolen et al., 1998; Heeb and Yahr, 2001). The MPOA occupies a pivotal position, because it is a region in which sexually related stimuli are summated and behavioral outputs relevant to the sexual response are generated. The essential role for MPOA in ejaculation has been documented in several experiments in which the two phases of ejaculation were abolished after MPOA lesion (Arendash and Gorski, 1983) and elicited upon chemical (Hull et al., 1992; Kitrey et al., 2007) or electrical (Marson and McKenna, 1994) in situ stimulations. Because MPOA does not project to the spinal cord, its action occurs through projections to other brain regions, such as the paraventricular hypothalamic nucleus (PVN) and the paragigantocellular nucleus (nPGi), identified as directly contacting the ejaculatory centers of the spinal cord (Simerly and Swanson, 1988; Murphy et al., 1999).

A description of the exact function of PVN in ejaculation is complex because of the several neuronal populations identified as regulating various neuroendocrine and autonomic responses and, more particularly, erection (Giuliano et al., 2001; Argiolas and Melis, 2004). Within the parvocellular part of the PVN, a group of oxytocinergic neurons has been shown to project to thoracolumbar and lumbosacral preganglionic autonomic neurons innervating pelvi-perineal viscera (Saper et al., 1976; Luiten et al., 1985). Another group of oxytocinergic neurons lying in the magnocellular division of the PVN sends axons to the posterior pituitary gland, where OT is released in blood circulation and acts as a hormone (Neumann et al., 1993). Bilateral lesion of the PVN did not prevent ejaculation in copulating male rats but reduced the weight of released seminal material (Ackerman et al., 1997), pointing out impaired emission. Behavioral study carried out in rats categorized according to their ejaculatory performance (ejaculation frequency and latency in a standardized copulatory test) led to the suggestion that a direct correlation exists between the proportion of PVN oxytocinergic neurons expressing c-Fos and the ejaculatory performance (Pattij et al., 2005). Both parvocellular and magnocellular oxytocinergic neuronal populations were found to be differentially activated in regard with ejaculatory performance. The role of each component on the ejaculatory response remains to be delineated although recent evidence showed that blockade of peripheral OT receptors (hormonal component) does not alter pharmacologically induced ejaculation (Clément et al., 2008).

Finally, another brain structure that probably exerts an excitatory role in the regulation of ejaculation is the lateral hypothalamus (LH). This brain area integrates forebrain limbic and autonomic nervous system inputs and has interconnections with MPOA, amygdala, and brainstem structures (for review, see Bernardis and Bellinger, 1993). Lesions of the anterior part of the LH in rats strongly affect the occurrence of ejaculation (Kippin et al., 2004). Experimental findings in the rat indicate that serotonin (5-HT), which is released in lateral hypothalamic area, increases as ejaculation occurs and is key in the activity of this structure (Lorrain et al., 1997).

3. Inhibitory Areas. An inhibitory role on ejaculation has been suggested for nPGi, which projects to preganglionic parasympathetic and somatic neurons as well as interneurons in the lumbosacral spinal cord (Marson and McKenna, 1992, 1996), on the basis of investigations using experimental models of expulsion reflex in rats (Marson and McKenna, 1990; Johnson and Hubscher, 1998). The lateral part of the nPGi seems to be more particularly involved (Johnson and Hubscher, 1998). In addition, selective lesion of 5-HT transporter-expressing neurons (the great majority of which are serotonergic) within the ventral medulla (including nPGi) suppresses the inhibitory tone of brain descending projections on expulsion reflex (Gravitt and Marson, 2007). From this set of data, it can be proposed that a group of neurons within the MPOA modulates the tonic inhibitory influence of nPGi serotonergic neurons on the expulsion reflex in response to peripheral sexual stimuli.

4. The Human Situation. Noninvasive functional imaging techniques have been used to examine the neurophysiological processes involved in the sexual response in humans. Of great interest regarding the brain activity associated with ejaculation are positron emission tomography (PET) studies that measured regional cerebral blood flow in healthy volunteers (Holstege et al., 2003; Georgiadis et al., 2007). A precise assessment of discriminating PET images led to the identification of cerebral structures activated or inhibited in relation to ejaculation. Increased activity was measured in the ventrolateral part of the left transition zone of midbrain and thalamus, in agreement with c-Fos experiments in animals. This probably reflects sensory processing associated with ejaculation. Higher activity was also found in the left dentate nucleus in the cerebellum during ejaculation, a response that was not observed in laboratory animals. Because activation of the dentate nucleus was correlated with striated pelvic floor muscle contractions

in women experiencing orgasm (Georgiadis et al., 2006), one can postulate that this region contributes to the elaboration of motor command to pelvi-perineal striated muscles responsible for sperm expulsion. Finally, marked decreased activity in prefrontal cortex was detected at the time of ejaculation, an effect that could not be assessed in c-Fos studies. Lesions of the prefrontal cortex are known to be responsible for sexual disinhibition (Aloni and Katz, 1999), and deactivation of this region has been observed in female subjects during orgasm induced by clitoral stimulation (Georgiadis et al., 2006). Therefore, diminished activity in the prefrontal cortex seen in men during ejaculation probably reflects removal of the inhibitory tone it exerts on ejaculatory response.

The above data collected in men do not make it possible to 1) establish causal link between brain activity and ejaculatory process and 2) distinguish between executive command of ejaculation and orgasmic feeling concomitant with ejaculation. In addition, because acquisition of PET images requires 120-s exposures, brain regions identified might also have been the result of events occurring immediately before and/or after ejaculation, such as high sexual arousal or sexual satiety. Further well designed experiments using functional magnetic resonance imaging with greater temporal resolution and including subjects with ejaculatory dysfunctions are necessary to provide a clearer picture of the human situation.

The existence of a CNS network intimately interconnected with a larger circuitry of the sexual response and that comprises several neuronal groups dedicated to the control of ejaculation implies the participation of various neurotransmitter systems. A better understanding of the neuropharmacology of ejaculation has emerged from animal studies but also from clinical observations.

III. Neuropharmacology of Ejaculation

Table 1 summarizes the major neurotransmitters involved in the control of ejaculation in CNS and periphery, their principal action, and the first molecular effectors.

A. Periphery

1. Adrenergic and Cholinergic Control. As described above, synergic activation of sympathetic and parasympathetic relevant pathways causes emission of seminal fluid into the urethra. Radioautographic detection of adrenergic receptors in rat and human prostate and bladder neck indicates that α_{1a} subtypes are predominant, although α_2- and β-adrenoreceptors have also been detected (Dubé et al., 1986; Chapple et al., 1989). Both α_1- and α_2-adrenoreceptors have been identified in urethra of various species, being mainly located in smooth muscle cells (α_1) and submucosa (α_2) (Monneron et al., 2000). Pharmacological investigations showed that contractions of the seminal tract and accessory sex glands elicited by sympathomimetic agents were blocked, at least partially, by α_1-adrenoreceptor antagonists (Stjernquist et al., 1983; Terasaki, 1989; Kolbeck and Steers, 1992; Kontani and Shiraoya, 2002). Cholinomimetic drugs are known to induce contraction of sex glands through stimulation of muscarinic receptors (Lepor and Kuhar, 1984; Terasaki, 1989). Moreover, by measuring fructose release as a marker of seminal vesicle secretion in vitro, Sjöstrand and Hammarström (1995) found that carbachol and acetylcholine trigger secretion, an effect reversed by the muscarinic antagonist scopolamine. However, the same observation was reported after electrical stimulation of the sympathetic hypogastric nerve, leading to the suggestion that a cholinergic component also mediates the sympathetic activation of secretory cells (Sjöstrand and Hammarström, 1995). This view is further supported by the fact that electrical stimulation of the parasympathetic pelvic nerve resulted in contraction of the prostate without any evidence of secretion (Watanabe et al., 1988).

2. Nitric Oxide. The crucial role of the gaseous neurotransmitter nitric oxide (NO) in peripheral physiology of penile erection is well documented (for review, see Andersson, 2001). NO, produced by NO synthase (chiefly the neuronal isoform), activates soluble guanylyl cyclase, which increases cGMP levels. Acting as a second messenger molecule, cGMP regulates the activity of calcium channels as well as intracellular contractile pro-

TABLE 1
Main neurotransmitters involved in the control of ejaculation and their major effects at different levels

Neurotransmitter	Brain	Spinal cord	Genital Tract
ATP			+ / $P2X_{1/2}$ (emission)
Acetylcholine			+ / M (emission and expulsion)
Dopamine	+ / $D_{2/3}$		
GABA		− / $GABA_{A/B}$	
Glutamate	+ / NMDA	+ / NMDA	
Noradrenaline			+ / α1 (emission)
Nitric oxide	+ / GC		+ / GC (emission)
Opioids	− / μ		
Oxytocin	+ / OTR	+ / OTR	+ / OTR (emission)
Serotonin	− / 5-HT1A/B/2C	+ / 5-HT2C/1A − / 5-HT1A/B?	− / 5-HT1A/B? (emission)
Substance P		+ / NK1	

+, excitatory effect on ejaculation; −, inhibitory effect on ejaculation; GC, guanylate cyclase; M, muscarinic receptor; OTR, oxytocin receptor; P2X, purinergic receptor subtype.

teins. This results in relaxation of corpus cavernosum smooth muscle cells essential for blood engorgement of the penis. However, the participation in ejaculation of peripheral NO, which represents a major component of the nonadrenergic/noncholinergic autonomic system, is less clear. Nitrergic fibers have been shown to innervate the entire seminal tract in various species, including human (Bloch et al., 1997; Sjöstrand et al., 1998; Uckert et al., 2003). Based on in vitro study of human seminal vesicles, activation of the NO-cGMP cascade has been suggested to reduce smooth muscle cell contraction (Machtens et al., 2003). In line with this is the observation that inhibitors of phosphodiesterase type 5 that block cGMP catabolism also reduce human seminal vesicle contractile activity in vitro (Uckert et al., 2009). However, as seen in section III.C.2, CNS has been advanced as the main site of action where NO acts in vivo to influence the ejaculatory process.

3. Oxytocin. In addition to being released into the blood from the pituitary gland, OT is also thought to be synthesized at the periphery in a paracrine/autocrine way, notably in the testes and the prostate (for review, see Gimpl and Fahrenholz, 2001). Oxytocin receptors have been found expressed in smooth muscle cells of epididymis (Filippi et al., 2002) and testis (Nicholson et al., 1984). Stimulation of OT receptors, which are positively coupled with phospholipase C, induces smooth muscle cell contraction through an increase in cytoplasmic calcium. In addition, OT stimulates the release of the procontractile peptide endothelin-1 in epididymis, thereby amplifying OT-induced smooth muscle cell contraction (Filippi et al., 2002). It was therefore proposed that OT in epididymis promotes spermatozoa transport into the vas deferens during the emission phase of ejaculation. This could explain the facilitation of ejaculation found in copulating rats after systemic delivery of OT (Arletti et al., 1985; Stoneham et al., 1985). Apparently supporting this view is the fact that, in rats as well as in men, plasma levels of OT do not show marked increase during sexual arousal but peak at the time of ejaculation (Stoneham et al., 1985; Carmichael et al., 1987; Murphy et al., 1987). However, the causative link between OT plasma levels and ejaculation could not be established with OT release in systemic circulation, which may be a consequence of ejaculation. Moreover, recent experiments in rats do not support a major role for peripheral OT receptors in occurrence of ejaculation (Clément et al., 2008) and rabbit, where the OT effect seems to be mediated by vasopressin 1A receptors (Gupta et al., 2008).

4. Purinergic System. P2X receptors are ion channels gated by ATP that are permeable to various cations including Na^+, K^+, and Ca^{2+}. Cotransmission of ATP and noradrenaline has received support from functional study in rodent vas deferens (Allcorn et al., 1986). Purinergic-2 (P2) receptors, which include ionotropic P2X and metabotropic P2Y subtypes, have been detected in the urogenital tract in different species including human. P2X1 isoform is found in the fibromuscular stroma of the prostate, and both P2X1 and P2X2 isoforms are present in high density in smooth muscle cells of epididymis, vas deferens, and seminal vesicle (Lee et al., 2000; Banks et al., 2006). In isolated organ bath experiments, it was shown that purinergic agonists induce contraction of vas deferens smooth muscle cells, whereas antagonists reduce contraction elicited by electrical-field stimulation (Banks et al., 2006). These results suggest that activation of P2X receptors in urogenital tract significantly contribute to the emission of sperm. However, evidence for the involvement of purinergic pathway in the control of ejaculation is lacking in more integrated models. Nevertheless, it is noteworthy that targeted deletion of the *P2X1* gene in male mice markedly diminishes fertility as a result of decreased number of spermatozoa in the ejaculate (Mulryan et al., 2000).

5. Serotonin. There are very few arguments in favor of the implication of peripheral 5-HT in ejaculation. Serotonergic neural fibers have been detected in prostate, seminal vesicle, vas deferens, and urethra in different species (Hanyu et al., 1987; Di Sant'Agnese et al., 1987). mRNAs for 5-HT1A, -1B, and -2C receptor subtypes were found in rat seminal vesicles and vas deferens (Kim and Paick, 2004), although their precise location (pre- or postsynaptic) is unknown. Functional investigations have shown that 5-HT counteracts neurally evoked contractions of seminal vesicle and vas deferens in vitro (Kim and Paick, 2004). Nevertheless, 5-HT acts primarily in CNS to modulate the ejaculatory response as described in sections III.B.4 and III.C.5.

6. Other Factors. Nonadrenergic/noncholinergic factors other than NO have also been identified throughout the seminal tract. Among them, vasoactive intestinal peptide and neuropeptide Y are the most common peptides in sex glands and vasa deferentia (Vaalasti et al., 1980; Stjernquist et al., 1983; Adrian et al., 1984). Vasoactive intestinal peptide and neuropeptide Y have been suggested to be colocalized with acetylcholine and noradrenaline, respectively in smooth muscle cells of vas deferens and seminal vesicle (Stjernquist et al., 1987). Other peptides, including enkephalin, SP, somatostatin, and calcitonin gene-related peptide, have also been found in the seminal tract (for review, see Dail, 1993). The functional role of those factors in the peripheral control of ejaculation remains unclear but is probably of secondary importance and will not be discussed further in this article.

B. Spinal Cord

1. GABA. GABA acts on receptors (A ionotropic and B metabotropic subtypes) that are widely distributed, so that most neurons in the CNS possess them. GABA A and B receptor sites and GABAergic pre- and postsynaptic projections have been reported in the sacral parasympathetic and Onuf's nuclei (Bowery et al., 1987; Ma-

goul et al., 1987). Pharmacological experiments targeting the spinal cord were undertaken to clarify the role of spinal GABA transmission in ejaculation. Baclofen, a GABA-B receptor agonist, does not prevent rats from copulating until ejaculation when administrated intrathecally at the L5-S1 spinal levels (Bitran et al., 1988). It has been demonstrated that the GABA-A agonist muscimol, injected into the LSt/SGE area, inhibits ejaculation induced by electrical microstimulation applied in this area (Borgdorff et al., 2008). Ejaculation was abolished when muscimol was delivered before but also during SGE stimulation, indicating that GABA-A receptor activation can prevent the triggering of ejaculation and can suppress ongoing ejaculation. In humans, baclofen is used in patients with spinal cord injuries to treat spasticity refractory to oral treatment. Intrathecal delivery of baclofen was reported to abolish or make more difficult ejaculation in this group of patients, an effect that was reversible upon treatment withdrawal (Denys et al., 1998; Lamotte and Cantalloube, 2007). GABA, through activation of GABA-A and -B receptors located in SGE region, seems to exert a strong inhibitory action on ejaculatory response.

2. Glutamate. Because glutamate is the main excitatory neurotransmitter in CNS, its contribution to the control of ejaculation can be postulated. Evidence of its participation at the spinal level has been provided only recently (Staudt et al., 2011). In mating rats, phosphorylation (i.e., activation) of the glutamate NMDA receptor subunit-1 in LSt neurons was found to be specifically related to the occurrence of ejaculation. An experimental model of expulsion reflex in spinalized anesthetized rats was used to further explore the mechanism of action of glutamate in LSt neurons. Activation of NMDA receptor subunit-1 was confirmed in this model. In addition, pharmacological manipulation with NMDA agonist and antagonist delivered locally into SGE/LSt area showed the important role of these receptors in the triggering of ejaculation. Binding of glutamate to NMDA receptors on LSt neurons may lead to ejaculation by promoting phosphorylation of extracellular signal-related kinases, which are markers of the mitogen-activated protein kinase signaling pathway (Staudt et al., 2010).

3. Oxytocin. The important contribution of spinal OT in erection, in particular OT released in the lumbosacral autonomic spinal network, has been documented in rats (Véronneau-Longueville et al., 1999; Giuliano et al., 2001). Experimental data supporting the role of spinal OT in ejaculation are scarce. Oxytocinergic projections from the parvocellular part of PVN have been shown to terminate close to lumbosacral preganglionic parasympathetic neurons innervating the urogenital tract (Tang et al., 1998), although a direct link with organs of ejaculation is not clearly established. Application of a nonselective cytotoxic agent into the PVN in rats did not abolish ejaculation but diminished the amount of seminal fluid ejaculated (Ackerman et al., 1997). More recent investigation of the effect of a peptide OT antagonist injected intrathecally at thoracolumbar and lumbosacral levels was performed in a model of pharmacologically induced ejaculation (Clément et al., 2008). The ejaculatory response, in particular the emission phase, was altered although not suppressed when the antagonist was delivered at L6-S1 level but not at T13-L1. As a whole, these data lead us to postulate that descending oxytocinergic projections from parvocellular PVN modulate lumbosacral spinal ejaculatory autonomic centers and influence emission phase of ejaculation.

4. Serotonin. The spinal cord receives a strong descending 5-HT innervation from the brain. More notably, a high density of 5-HT fibers has been reported in the vicinity of motor neurons in rat Onuf's nucleus (Tang et al., 1998). In addition, 5-HT immunoreactivity was found in the intermediolateral cell column in thoracic levels and in the sacral parasympathetic nucleus (Bowker et al., 1982; Ranson et al., 2003). Soma of the serotonergic neurons descending projections to the ventral horn have been localized in raphe obscurus and pallidus nuclei, and nPGi (Basbaum et al., 1978; Bowker et al., 1982; Marson and McKenna, 1996). Projections into the dorsal horn mainly originate in neurons of the raphe magnus nucleus and reticular formation (Basbaum et al., 1978). To date, three 5-HT subtypes have been detected in the spinal network involved in ejaculation. 5-HT1A, -1B, and -2C receptors are densely expressed in the sacral parasympathetic nucleus and motoneurons of Onuf's nucleus (Marlier et al., 1991; Thor et al., 1993; Ridet et al., 1994; Bancila et al., 1999). In addition, high density of 5-HT1B receptors has been described in lamina X of the lumbar spinal cord, which includes SGE area (Marlier et al., 1991). After a series of experiments investigating the role of 5-HT in a model of expulsion reflex in rat (urethrogenital reflex), it was suggested that 5-HT released in lumbosacral segments from terminals of neurons lying in the ventrolateral medulla exerts an inhibitory tone on ejaculation (Marson and McKenna, 1990, 1992; Gravitt and Marson, 2007). However, 5-HT spinal control of ejaculation seems multimodal and occurs at multiple levels of the spinal cord, as suggested by other findings rather supporting a proejaculatory role of spinal 5-HT. The amphetamine derivative *p*-chloroamphetamine (PCA), which releases catecholamines and 5-HT from monoaminergic nerve terminals, triggers ejaculation in conscious and anesthetized rats (Rènyi, 1985; Yonezawa et al., 2000; Clément et al., 2006a). Pharmacological competition showed that the primary role in mediating the activity of PCA on ejaculation is played by 5-HT, whereas noradrenaline seems to be of secondary importance (Rènyi, 1985). It is noteworthy that ejaculation was still obtained when PCA was delivered to rats subjected to acute spinal cord complete section at T8-T9 level (Yonezawa et al., 2000; Stafford et al., 2006). Furthermore, in another experimental paradigm of ejaculatory

reflex (i.e., pudendal motoneuron reflex discharges), 5-HT and the SSRI dapoxetine delivered in the subarachnoidal space at L6-S1 levels were found to enhance this reflex (Clément et al., 2007b). The proejaculatory action of PCA is likely to be mediated by lumbosacral 5-HT2C receptors, with possible potentiation by 5-HT1A receptors (Stafford et al., 2006). Because of the multilevel and multimodal action of spinal 5-HT, defining its precise role in ejaculation is challenging and requires further research.

5. Substance P. The principal function of the undecapeptide SP synthesized in primary sensory neurons is to carry sensory information from the periphery to the CNS. A putative role for spinal SP in ejaculation was first inferred from the immunohistochemical demonstration that its main receptor (NK1) is expressed by LSt neurons (Truitt and Coolen, 2002). These authors also studied the functional consequences of selective destruction of LSt by means of the neurotoxin saporin conjugated to a ligand of NK1 receptor delivered in the L3-L4 centro-medial region. Abolition of ejaculation was reported in copulating male rats, whereas other aspects of sexual function were not altered. However, these data do not elucidate the role of SP neurotransmission. First evidence of the modulatory activity of lumbar spinal NK1 receptors was provided when ejaculation was pharmacologically induced in anesthetized rat (Clement et al., 2009a). A selective NK1 antagonist delivered intrathecally at the L3-L4 level reduced ejaculation occurrence. The tachykinin receptor NK1 is coupled to G protein, and its activation stimulates a variety of effector mechanisms via generation of intracellular second messengers (phosphatidyl inositol, arachidonic acid, and cAMP). Alternately, SP is coexpressed with glutamate in primary afferents (De Felipe et al., 1998), and activation of NK1 receptor amplifies glutamatergic excitatory postsynaptic potentials (Adelson et al., 2009). Given the importance of glutamate in LSt excitation (see section III.B.2), the latest mechanism of action deserves further investigation.

6. Other Factors. A variety of neuropeptides have been detected in the ejaculatory spinal network. Nevertheless, for most of them, functional evidence for their involvement in the control of ejaculation is tenuous or lacking.

Neurons lying in the SGE area and synthesizing the cholecystokinin octapeptide fragment (CCK-8) have been found to project to thalamic regions, including SPFp (Ju et al., 1987). As such, they can be regarded as LSt neurons. A large portion of CCK-8 containing neurons cosynthesizes galanin and is specifically activated with ejaculation in male rats (Truitt et al., 2003). The activity of spinal CCK-8 in ejaculation is still to be clarified, although it may participate, together with galanin, to the transmission of ejaculation-related sensory messages toward integrative sites of the thalamus where CCK receptors (G protein-coupled) have been detected (Niehoff, 1989).

LSt neurons are known to be galaninergic and to project to thalamic structures (Ju et al., 1987). As specified above, the majority of these cells coexpresses CCK-8. Further neuroanatomical investigations revealed in the rat that galaninergic projections of LSt constitute a unique input to the medial subdivision of SPFp, which contains neurons specifically activated with ejaculation (Coolen et al., 2003). It can therefore be postulated that the LSt-SPFp galaninergic connection is a major pathway in the relay of ejaculation-related sensory information. Three galanin receptor subtypes coupled to protein G mediate the action of galanin in CNS, although their specific function remains to be fully elucidated (Branchek et al., 2000). Studying the exact contribution of galanin released in SPFp from LSt terminals in the ejaculatory response is needed.

Gastrin-releasing peptide (GRP) is a bombesin-like peptide that binds to three G protein-coupled receptors characterized to date. A population of neurons within the SGE in rats has been reported to contain GRP and to send projections to the sacral parasympathetic nucleus and Onuf's nucleus, where GRP receptors (GRP-preferring subtype) were identified (Sakamoto et al., 2008). Pharmacological manipulations using selective agonist and antagonist of this GRP receptor subtype showed that the GRP spinal pathway controls ejaculation but also erection in rats (Sakamoto et al., 2008).

Two different neuronal populations containing the endogenous opioid peptide enkephalin have been identified in lamina X in rat lumbar spinal cord segments (Nicholas et al., 1999). The most rostral population, extending from L1 to L4-L5, also expressed galanin and CCK (octa and tetrapeptide) and could be LSt neurons. The exact role for this enkephalinergic pathway in ejaculation remains to be delineated.

C. Brain

1. Dopamine. The incertohypothalamic, nigrostriatal, and mesolimbic dopaminergic pathways play a facilitating role in male sexual behavior (for review, see Hull et al., 2004; Peeters and Giuliano, 2008). However, because the incertohypothalamic pathway that includes MPOA is more particularly involved in the control of ejaculatory response, only this system is addressed here. Soma of dopaminergic neurons of the incertohypothalamic system are located in the rostral part of the medial zona incerta and in the rostral periventricular nucleus. Their projections terminate in the hypothalamus, the lateral preoptic area and the MPOA, the parvocellular region of the PVN, the thalamus, and the midbrain central gray.

The first evidence supporting the facilitating effect of dopamine on ejaculation were provided in male rats treated with apomorphine, a nonselective dopamine receptor agonist, and L-DOPA, the synthesis precursor of

dopamine (Tagliamonte et al., 1974; Paglietti et al., 1978). Later, the incertohypothalamic pathway was targeted using microinjection of apomorphine into the MPOA in male rats (Hull et al., 1986). This resulted in shortening of ejaculation latency and increased number of ejaculations and copulatory rate. The crucial role of MPOA was further confirmed by the observation that increase in dopamine extracellular levels was correlated with a decrease in the latency of ejaculation and an increase in the number of mounts, intromissions, and ejaculations (Putnam et al., 2003).

Five subtypes of mammalian dopamine receptors have been identified, cloned, fully characterized, and classified as follows: D_1-like receptors (D_1 and D_5) and D_2-like receptors (D_2, D_3,and D_4). Dopamine receptors are G-protein-coupled receptors, the D_1-like subtypes stimulating cAMP accumulation and the D_2-like subtypes inhibiting it (for review, see Neve et al., 2004). Among all types of dopamine receptors, only D_2 and D_3 subtypes can be presynaptic autoreceptors regulating dopamine release and metabolism (Mercuri et al., 1997). High density of D_1 receptor has been found in limbic system, hypothalamus, thalamus, and PVN (Mengod et al., 1989; Czyrak et al., 2000). D_2-like receptors have also been detected in limbic areas, hypothalamus, and thalamus. The presence of D_2/D_3 receptors using radiolabeled ligand in MeA, BNST, and MPOA can be emphasized (Yokoyama et al., 1994; Bancroft et al., 1998).

A series of experiments was carried out to describe the functional role of dopamine receptor subtypes in ejaculation. Specific action on one of the five dopamine receptor subtypes identified to date using selective ligands has long been challenging. First findings in copulating rats showed that MPOA D_1- and D_2-like receptors have opposite roles in the control of ejaculation. The former facilitates erectile mechanisms and enhances the rate of copulation, whereas the latter facilitates ejaculation (Hull et al., 1989; Markowski et al., 1994). It was thus suggested that MPOA D_1- and D_2-like receptor influences are related to the level of dopamine stimulation, with an evolution from the copulatory phase (mediated by D_1 receptors) to the ejaculatory phase (mediated by D_2-like receptors) as dopamine concentration increases in this area (Hull et al., 1992). While more selective ligands became available, it was found that the D_2/D_3 receptor agonist 7-OH-DPAT enhanced ejaculatory behavior in rats (Alhenius and Larsson, 1995; Ferrari and Giuliani, 1996). This compound is even capable of triggering ejaculation in anesthetized rats by acting in the MPOA (Clément et al., 2007a; Kitrey et al., 2007). Finally, the most recent pharmacological investigations indicate that blockade of D_3 receptors with highly selective antagonist prolongs ejaculation latency and postejaculatory refractory period, probably by specifically inhibiting the expulsion phase of ejaculation (Clément et al., 2009b). Therefore, a particular component of the brain dopaminergic pathway seems to be especially involved in the control of a specific aspect of the ejaculatory response.

2. Nitric Oxide and Glutamate. The freely diffusing gaseous molecule NO is becoming recognized as one of the important intracellular messengers in the brain. The neuronal isoform of NO synthase is the main source of NO in the brain and has been notably detected in the MPOA (Bhat et al., 1995).

Several lines of evidence support the involvement of NO synthesized in MPOA in the male sexual response. Local delivery of the NO synthesis precursor L-arginine stimulates sexual behavior in copulating rats, an effect reversed by a NO synthase inhibitor (Sato et al., 1998). Moreover, microinjection into the MPOA of a NO synthase inhibitor impairs copulation and abolishes ejaculation (Lagoda et al., 2004). Further pharmacological experiments showed that the effect of NO is mediated by increased production of cGMP through activation of guanylyl cyclase (Sato and Hull, 2006). In an effort to better understand the mechanism of action of NO produced in MPOA, it was advanced that NO is a major activator of dopamine release in this structure (Hull and Dominguez, 2006). Indeed, monitoring of dopamine extracellular content in MPOA of male rats demonstrated that L-arginine locally infused causes increase in dopamine release (Lorrain and Hull, 1993). In addition, increased MPOA dopamine extracellular concentration during copulation is suppressed by NO synthase and guanylyl cyclase inhibitors (Lorrain et al., 1996; Sato and Hull, 2006). A major excitatory mechanism of NO synthesis is glutamate, which, through binding to NMDA receptors, activates calmodulin, the key factor for NO synthase activity. Accordingly, intra-MPOA administration of a NMDA receptor antagonist exerts effects on male rat sexual behavior and dopamine release similar to those obtained with a NO synthase inhibitor (Dominguez et al., 2004; Vigdorchik et al., 2012). The important role of MPOA glutamate was reinforced by a microdialysis study showing a peak in extracellular glutamate concentration at the time of ejaculation (Dominguez et al., 2006). In line with this is the observation that microinjection of an NMDA agonist into the MPOA of anesthetized rat initiates rhythmic contractions of bulbospongiosus muscle (Marson and McKenna, 1994).

3. Opioids. Participation of endogenous opioids in the regulation of the different aspects of sexual behavior is supported by experimental evidence gathered from the male rat. In general, opioids have inhibitory effects on consummatory aspects of mating. Systemic administration of the opioid agonist morphine decreases the proportion of males that copulate, increases mount and intromission latencies, and decreases the frequency of mounts and intromissions (Agmo and Paredes, 1988). In contrast, administration of the opioid receptor antagonists naloxone and naltrexone facilitates consummatory aspects of sexual behavior by increasing the percentage of males that copulate, by decreasing mount, intromis-

sion, and ejaculation latencies, and increasing the number of mounts and intromissions achieved before ejaculation (Van Furth et al., 1994). In addition, opioids are involved in the initiation of sexual behavior after ejaculation, because naloxone extends the postejaculatory refractoriness (Szechtman et al., 1981; Van Furth et al., 1994) and inhibits resumption of mating in sexually sated male rats after the reintroduction of a female rat (Miller and Baum, 1987). Finally, opioids play a role in reward-related aspects of ejaculation, because naloxone also blocks the expression of ejaculation-induced place preference (Agmo and Berenfeld, 1990; Mehrara and Baum, 1990).

In view of the pharmacodynamic properties of the ligands used in the rat sexual behavior studies performed to date, mainly brain μ-opioid receptor subtypes seem to be involved in the regulation of ejaculation and its rewarding aspect. This is supported by the evidence that μ-opioid receptor subtype expressed in MPOA is activated during male sexual behavior (Coolen et al., 2004). However, the role of the other opioid receptor subtypes (there are four subtypes identified to date) is unclear, and it would be of great interest to figure out whether one subtype is specifically involved in the control of ejaculation.

4. Oxytocin. The involvement of brain OT in male sexual functions is well documented; notably, this neuropeptide was found to be one of the most potent agents to induce penile erection in various animal species (for review, see Argiolas and Melis, 1995). Two different oxytocinergic systems exist in the brain (for review, see Gimpl and Fahrenholz, 2001). First, hypothalamic magnocellular neurons (in PVN and supraoptic nucleus) synthesize OT, which is stored in the posterior lobe (neurohypophysis) of the pituitary gland and released into systemic circulation. The second pathway is composed of parvocellular neurons of the PVN that project in multiple regions in the rat brain (including bed nucleus of the stria terminalis, medial amygdala, and MPOA) and spinal cord (see section II.C.2). Accordingly, OT receptors, which are identical in CNS and periphery, have been found in these sites. Oxytocin autoreceptors have been characterized in magnocellular neurons, and their activation has been suggested to exert a positive feedback on OT release (Dayanithi et al., 2000).

A key role for brain OT in the control of ejaculation has been demonstrated. Infused into the cerebral ventricle of a male rat free to copulate with a receptive female, OT facilitates ejaculatory behavior by shortening ejaculation latency and postejaculatory refractory period (Arletti et al., 1985). Intracerebroventricular administration of a potent OT antagonist impairs sexual performance in experienced male rats in the presence of a receptive female by decreasing the intromission frequency and abolishing ejaculation at doses failing to modify any other behavioral parameters (Argiolas et al., 1988). In addition, delivery of a selective OT receptor antagonist into cerebral ventricle reverses ejaculation induced by 7-OH-DPAT in anesthetized rat (Clément et al., 2008).

Other studies have clearly evidenced the role of central OT in the postejaculatory refractoriness. In rats, OT concentrations in plasma and cerebrospinal fluid increase after ejaculation and are elevated during the postejaculatory refractory period (Stoneham et al., 1985; Hughes et al., 1987). In men also, plasma OT was reported to start increasing before ejaculation and to be significantly higher at the time of ejaculation (Carmichael et al., 1987; Murphy et al., 1987).

The precise mechanism of action of cerebral OT in ejaculatory response is to be clarified, although it can be supposed that it acts through activation of OT hetero- and autoreceptors located in brain ejaculatory circuit but also via modulation of 5-HT (de Jong et al., 2007) and dopamine neurotransmission (Clément et al., 2008). Stimulation of OT receptors activates different GTP-protein-related intracellular signal pathways (for review, see Gimpl and Fahrenholz, 2001). The predominant mechanism consists of G_q-mediated phospholipase C activation, although coupling of OT receptor with G_s and G_i also causes stimulation and inhibition of adenylyl cyclase, respectively.

5. Serotonin. The function of brain 5-HT in the control of ejaculation has been evaluated in several behavioral studies (for review, see Hull et al., 2004; Giuliano, 2007a). Upon local injection into serotonergic projection fields in forebrain and MPOA of male rats, 5-HT inhibits sexual behavior and, more notably, delays ejaculation (Verma et al., 1989; Hillegaart et al., 1991; Fernández-Guasti et al., 1992). Conversely, ejaculatory behavior was reported as facilitated when 5-HT was microinjected into raphe nuclei containing serotonergic cell bodies (Hillegaart et al., 1989). In addition, extracellular 5-HT levels were found to be increased in LH after ejaculation in copulating male rats (Lorrain et al., 1997). This observation [together with the fact that local microinjection of SSRIs into LH, which results in a higher amount of intrasynaptic 5-HT in this area, inhibits sexual behavior (Lorrain et al., 1997)] supports the hypothesis that 5-HT contributes to the refractory period immediately after ejaculation.

The delaying effect of long-term administration of SSRIs on ejaculation has been demonstrated in several behavioral studies carried out in rats (for review, see Giuliano, 2007a). From these data, it can be concluded that long-term use of SSRIs substantially inhibits copulatory behavior without affecting sexual motivation, as measured by the time the male takes to engage in sexual interaction with a receptive female (Cantor et al., 1999; Mos et al., 1999; Frank et al., 2000; Waldinger et al., 2002). More particularly, ejaculation latency and postejaculatory refractory period were found to be dose dependently increased after daily SSRI treatment, although drug-to-drug differences in the amplitude of

changes were reported (Mos et al., 1999; Waldinger et al., 2002). The fact that long-term exposure to SSRIs leads to a global increase in serotonergic tone explains the inhibitory action of SSRIs on ejaculation. However, key points, including brain site(s) of action and 5-HT receptor subtype(s) involved, are not fully delineated. Findings in rats suggest that nPGi, and more particularly the lateral division, is crucial for the action of SSRIs, although it is still not clear whether this brain structure is a site of action or an essential component situated downstream (Yells et al., 1994; Clément et al., 2007b).

Selective ligands for the different 5-HT receptor subtypes were used to clarify the mechanism of action of brain 5-HT. The 5-HT1A-selective agonist 8-OH-DPAT has a facilitator effect on ejaculation after systemic delivery in rats (Hillegaart and Ahlenius, 1998; Rowland and Houtsmuller, 1998). This proejaculatory activity was observed after microinjection of 8-OH-DPAT into the median raphe nucleus or nucleus accumbens (Hillegaart et al., 1991; Fernández-Guasti et al., 1992). A plausible mechanism explaining 8-OH-DPAT effect involves 5-HT1A somatodendritic autoreceptors, which are expressed on cell bodies of serotonergic neurons. Stimulation of these autoreceptors is responsible for a decrease in neuronal firing and consequently in the amount of 5-HT released in terminal areas, notably in forebrain and hypothalamus (Sharp et al., 1989; Bonvento et al., 1992). However, these results have to be interpreted cautiously, in view of more recent findings strongly suggesting that brain dopamine D_2-like receptors mediate the proejaculatory action of 8-OH-DPAT (Matuszewich et al., 1999; Clément et al., 2006b).

Agonists of 5HT1B receptors impair ejaculation when given systemically to male rats free to copulate (Fernández-Guasti et al., 1992; Hillegaart and Ahlenius, 1998). Moreover, blockade of 5-HT1B receptors reverses the inhibitory action of the 5-HT metabolite precursor 5-hydroxytryptophan on ejaculation (Ahlenius and Larsson, 1998). 5-HT1B receptors have been detected in several sites of the rat hypothalamus, including MPOA and LH (Makarenko et al., 2002), although the effect of their stimulation on male sexual behavior is unknown because effects of local brain delivery have not been tested. Understanding of 5-HT1B precise role is further hindered by the fact that this receptor subtype, a G protein-coupled receptor inhibiting adenylate cyclase, can be a presynaptic autoreceptor or a postsynaptic heteroreceptor (Barnes and Sharp, 1999).

Involvement of 5-HT2C receptors in mediating cerebral 5-HT control on ejaculation has been proposed from pharmacological manipulations during male rat sexual behavior experiments. Activation of 5-HT2C receptor increases the synthesis of diacylglycerol and inositol triphosphate via G-protein-coupled mechanism (Barnes and Sharp, 1999). Short-term systemic administration of a 5HT2A/2C agonist resulted in inhibition of ejaculation, an effect that was reversed with a 5-HT2C selective antagonist (Foreman et al., 1989). High density of 5-HT2C receptors has been described in the limbic areas nucleus accumbens and amygdala (Barnes and Sharp, 1999), although the exact site at which 5-HT2C ligands act is to be delineated.

6. Other Factors. A variety of neuropeptides acting as neuromediators or neuromodulators in the brain have been reported to be involved in male sexual functions (for review, see Argiolas, 1999). For only a few of them has a role in the control of ejaculation been ascribed.

Adrenocorticotropin, α-melanocyte stimulating hormone (α-MSH), and related peptides (adrenocorticotropin-MSH–related peptides) derived from proopiomelanocortin also have been reported to induce ejaculation and erection after delivery into cerebral ventricle (Ferrari et al., 1963; Bertolini et al., 1969). In addition, intracerebroventricular injection of adrenocorticotropin-MSH–related peptides to male rats before copulation reduces the ejaculatory threshold (i.e., the number of intromissions preceding ejaculation) and shortens ejaculation latency (Bertolini et al., 1975). Further exploration identified MPOA as a site of action for α-MSH-related peptides (Hughes et al., 1988). At least five subtypes of functional high-affinity receptors for adrenocorticotropin-MSH-related peptides have been described as positively coupled to adenylyl cyclase and found in several hypothalamic areas (BNST, MPOA, and lateral hypothalamic area) of rats (Mountjoy et al., 1992; Roselli-Rehfuss et al., 1993; Konda et al., 1994). Additional experiments have to be done to understand the mechanism of action of adrenocorticotropin-MSH–related peptides in the control of ejaculation.

The fact that LSt terminals in the SPFp express CCK-8 leads to the hypothesis that this neuropeptide participates in the control of the ejaculatory process. However, studies assessing the functional role of CCK-8 (and other CCK polypeptides) are scarce and conflicting. Upon delivery into cerebral ventricle or MPOA, CCK-8 was not found to affect sexual performance of sexually active male rats (Bloch et al., 1988; Dornan and Malsbury, 1989), whereas another study reported facilitation of ejaculation when CCK-8 was administered subcutaneously (Pfaus and Phillips, 1987). Targeting SPFp with CCK-8 or its analogs would clarify its role in the ejaculatory response.

Ascending galaninergic projections of the LSt neurons to the SPFp are well characterized in the rat. However, the effects on ejaculation of galanin receptor ligands in this brain site have not been assessed so far. It was reported that upon intracerebroventricular delivery, galanin inhibited sexual behavior, all aspects being affected (arousal, motivation, and consummatory), whereas an antagonist enhanced sexual behavior (Poggioli et al., 1992; Benelli et al., 1994). In contrast, targeting the medial preoptic nucleus, a subdivision of the MPOA, with galanin was shown to facilitate sexual be-

havior, including motivation and consummatory indexes (Bloch et al., 1993). It seems, therefore, that activity of brain galanin on male sexual response depends on its site of action, and a better understanding of the role this neuropeptide plays in the control of ejaculation requires further experiments focused on SPFp.

The tuberoinfundibular peptide 39 (TIP39) is a neuropeptide of 39 amino acid residues that stimulates cGMP production after binding to parathyroid hormone-2 receptor (Usdin et al., 1999). The distribution of cell bodies containing TIP39 is restricted to three major areas of the thalamus (including SPFp) and pons, whereas TIP39 fibers are widespread throughout the brain and spinal cord. In male rats free to copulate, neurons lying in the medial subdivision of the SPFp are specifically activated in ejaculating animals (see section II.C.1). Approximately 15% of these activated neurons expressed TIP39, and 50 to 70% (depending on the number of ejaculations rats display) of TIP39-containing neurons are activated in this paradigm (Wang et al., 2006). The precise role of TIP39 in ejaculation remains unclear, and which CNS areas receive projections from TIP39-containing neurons in medial SPFp is unknown. However, medial SPFp occupies a pivotal position in the brain circuitry involved in ejaculation, and it is therefore possible that TIP39 plays a regulatory role in this process.

IV. Pharmacology of Current and Future Therapies for Premature Ejaculation

A. Pathophysiology of Premature Ejaculation

It should be emphasized that in PE, there is nothing that may justifiably be described as a deficiency. Each physiological event participating to ejaculation, including emission and expulsion, occurs correctly and synchronically in PE. In this way, PE clearly differs from other sexual medicine conditions, such as erectile dysfunction, for which a pathophysiological mechanism can often be identified, either vascular, neural, tissular, or mixed. What can be regarded as a pathologic condition in PE is the lack of control on ejaculation triggering. Depending on the timing of occurrence of PE, it can be classified as lifelong or acquired.

1. Lifelong Premature Ejaculation. PE is classified as lifelong or primary if it is present at almost every intercourse from the first sexual encounter onwards. It has been proposed that the persistently short intravaginal ejaculation latency times (IELTs) in men with lifelong PE are associated with diminished 5-HT neurotransmission, a hyperfunction of 5-HT1A receptors, and/or a hypofunction of 5-HT2C receptors (Waldinger et al., 1998). Such a pathophysiological hypothesis needs to be scientifically substantiated. The existence of a genetic component for lifelong PE could support the fact there are inherited differences in ejaculatory threshold. The allele of the polymorphic 5-HT transporter promoter region gene has been studied in a few genetic studies, different methods providing conflicting results (for review, see Buvat, 2011). It has recently been proposed that serotonergic genetic polymorphisms may be found only in men with PE who respond to SSRI treatment with an ejaculation delay (Waldinger, 2011). Overall genetic predisposition, which probably influences central 5-HT neurotransmission, should be considered as a hereditary susceptibility to a short IELT that needs, in most cases, to be maintained and heightened by psychological/environmental factors to lead to PE, because genetic effects represent only approximately 30% of the condition variance (Buvat, 2011). Serotonin dysregulation as an etiological hypothesis for PE explains only a small percentage (2–5%) of complaints of PE in the general population (Waldinger and Schweitzer, 2008). The role of penile hypersensitivity as a possible etiology of PE is controversial and is not evidence-based.

2. Acquired Premature Ejaculation. PE is classified as acquired or secondary if it develops after a period of previously normal control of ejaculation. A range of psychological factors may precipitate or maintain PE. These factors can be divided into predisposing or historical factors (e.g., sexual abuse, attitude toward sex in the home), individual psychological factors (e.g., body image, depression, performance anxiety, alexithymia), or relationship factors (e.g., intimacy, anger) (Althof et al., 2010). It has indeed been reported that IELT depends on a variety of contextual, psychological-behavioral, and relationship variables (Rowland and Cooper, 2005). Thirty percent or more of subjects with erectile dysfunction also experience PE (Laumann et al., 2005). Men with erectile dysfunction may intentionally "rush" intercourse to prevent early detumescence of erection, resulting in rapid ejaculation. This may be compounded by the presence of high levels of performance anxiety related to the erectile dysfunction, which serves only to worsen PE (for review, see Althof et al., 2010). Evidence has been provided for an association between hyperthyroidism and acquired PE in a few patients; nevertheless, the data linking thyroid hormones and ejaculatory dysfunction is inconsistent (for review, see Althof et al., 2010). Prostatic inflammation/chronic prostatitis might be involved in some cases (Lotti et al., 2009). Considering the role of the prostate in the ejaculatory mechanism, a direct influence of the local inflammation in the pathogenesis of some cases of acquired PE seems likely (for review, see Althof et al., 2010).

B. Current Pharmacological Treatments for Premature Ejaculation

Psychological counseling and behavioral methods have long been the only therapeutic management of PE. Psychological-behavioral approaches can benefit PE, although robust evidence of their efficacy is lacking (Hatzimouratidis et al., 2010). Moreover, because those approaches are time-consuming and require the contin-

uous participation of the partner, compliance is a major issue in lifelong PE. Recent advances in the understanding of the neurobiology of ejaculation have led to the identification of pharmacological targets that can be manipulated to relieve PE. This eventually resulted in the development of the first authorized medicine for PE (dapoxetine). The ideal pharmacological treatment of PE would increase ejaculation latency time without impairing the physiology of ejaculation and would be a fast-acting, well tolerated agent effective when taken as needed. Accordingly, any pharmacological agent with central or peripheral mechanism of action that is delaying ejaculation is a drug candidate for the treatment of PE.

1. Long-Term Use of Selective Serotonin-Reuptake Inhibitors and Clomipramine. Ejaculatory disturbances are consistent adverse effects of SSRIs and include, most commonly, delayed ejaculation and, less commonly, anejaculation. Because of the attendant stigmatization of sexual dysfunction and thus its under-reporting, the prevalence of delayed ejaculation is probably higher than the values in the literature might suggest (Lane, 1997). By contrast, a rebound PE syndrome after crSSRI withdrawal has been described previously (Adson and Kotlyar, 2003). Although it is certainly a side effect of crSSRI treatment, delayed ejaculation is not always perceived negatively as an adverse event (Rosen et al., 1999). In men with PE, a delayed time to ejaculation is highly desirable, thus leading to the "off-label" long-term use of SSRIs for PE. Despite the beneficial effect of crSSRIs in the treatment of PE, the mechanism of action has not been fully established. Indeed, the proposed mechanism of action remains conjectural and predicated (Giuliano, 2007a). The functions of 5-HT in the CNS are controlled by many factors, including the 5-HT transporter and somatodendritic (5-HT1A) autoreceptors. The 5-HT transporter removes 5-HT from the synaptic cleft, whereas the 5-HT1A autoreceptor modulates the firing rate of serotonergic neurons (for review, see Stamford et al., 2000). Activation of the 5-HT1A receptor by released 5-HT initiates a negative feedback process that reduces 5-HT cell firing and thus rebalances the system. At the level of the nerve terminal, there is further local feedback control by 5-HT1B autoreceptors; activation of these autoreceptors reduces synaptic 5-HT levels. Under normal physiological circumstances, the transporter functions to limit the "tone" at the autoreceptors. Enhanced activation of the 5-HT2C receptor is thought to underpin several of the side effects of SSRIs, including delayed ejaculation. A similar rationale is thought to explain the actions of crSSRIs in PE (Waldinger et al., 1998). During normal sexual functioning, the brain 5-HT-mediated system exerts an inhibitory effect on ejaculation; therefore, agents that enhance the transmission of 5-HT (e.g., SSRIs) increase this effect.

With the exceptions given below, a therapeutic benefit of SSRIs is only reported after 1 to 2 weeks of daily dosing. By analogy with depression, it is assumed that broadly similar neurochemical changes underlie the delay of ejaculation induced by crSSRIs. To some degree, this is consistent with the known proejaculatory effect of 5-HT1A receptor agonists. In the serotonergic neuron, 8-OH-DPAT binds to 5-HT1A autoreceptors, inhibiting the traffic in the descending serotonergic neurons and thereby diminishing 5-HT-mediated tone at the terminal. There are, however, some striking differences between the efficacy of crSSRIs in PE and depression. Most notably, there is a mismatch between antidepressant and antiejaculatory potency. Whereas crSSRIs are broadly equipotent as antidepressants at clinical doses, this is not true in PE. Paroxetine seems more effective at delaying ejaculation than other SSRIs (Montejo-González et al., 1997; Waldinger et al., 2004). Although SSRIs have varying affinities for different receptors, including the noradrenaline and dopamine transporters, that might help to explain their differing efficacy in delaying ejaculation if administered chronically, the exact site in the neurological circuitry that these drugs target in PE is unknown.

Daily treatment with off-label doses of 10 to 40 mg of paroxetine, 12.5 to 50 mg of clomipramine, 50 to 200 mg of sertraline, 20 to 40 mg of fluoxetine, or 20 to 40 mg of citalopram is usually effective in delaying ejaculation (Waldinger et al., 1994; Althof et al., 1995; Kara et al., 1996; McMahon, 1998; Atmaca et al., 2002). A meta-analysis of published data suggests that paroxetine exerts the strongest ejaculation delay, increasing IELT approximately 8.8-fold over baseline (Waldinger, 2003). Ejaculation delay usually occurs within 5 to 10 days of starting treatment, but the full therapeutic effect may require 2 to 3 weeks of treatment and is usually sustained during long-term use (McMahon, 2002). Adverse effects are usually minor, start in the first week of treatment, and may gradually disappear within 2 to 3 weeks. They include fatigue, yawning, mild nausea, diarrhea, or perspiration. Hypoactive desire and erectile dysfunction are infrequently reported and appear to have a lower incidence in nondepressed PE men compared with depressed men treated with crSSRIs (Waldinger, 2007).

Clomipramine is a tricyclic antidepressant that inhibits the uptake of noradrenaline and 5-HT by adrenergic and serotonergic neurons (Gur et al., 1999). Continuous dosing with clomipramine significantly lengthened IELT compared with placebo, as measured by stopwatch assessment in a randomized, placebo-controlled crossover trial in 36 men with PE (Kim and Seo, 1998). Daily treatment with 12.5 to 50 mg of clomipramine is usually effective in delaying ejaculation, IELT being increased up to 6-fold (for review, see Porst, 2011). Side effects associated with the use of clomipramine in men with PE included drowsiness, nausea, dizziness, dry mouth, and erectile dysfunction (Montague et al., 2004). According to ISSM, there is level 1a evidence to support the efficacy and safety of off-label daily dosing of the SSRIs

paroxetine, sertraline, citalopram, and fluoxetine and the tricyclic clomipramine for the treatment of lifelong and acquired PE (Althof et al., 2010).

2. Dapoxetine. Dapoxetine hydrochloride is a recently developed short-acting SSRI with a pharmacokinetic profile suggesting a role as an on-demand treatment for PE with a rapid T_{max} (1.3 h) and a short half-life (95% clearance rate after 24 h) (Modi et al., 2006). Dapoxetine has been investigated in more than 6000 subjects and has been recently approved in various countries for the on demand treatment of PE (Hellstrom, 2009). Both available doses of dapoxetine (30 and 60 mg) have shown 2.5- and 3.0-fold increases, respectively, in IELT overall, rising to 3.4- and 4.3-fold, respectively, in patients with baseline average IELT <0.5 min (McMahon et al., 2011). In randomized clinical trials, dapoxetine 30 or 60 mg taken 1 to 2 h before intercourse was effective from the first dose on IELT and also reported to increase ejaculatory control, decrease distress, and increase satisfaction. Dapoxetine has shown a similar efficacy profile in men with lifelong and acquired PE (Porst et al., 2010).

The mechanism of action of short-acting SSRIs in PE is still speculative. Dapoxetine resembles the antidepressant SSRIs in the following ways: the drug binds specifically to the 5-HT reuptake transporter at subnanomolar levels, has only a limited affinity for 5-HT receptors, and is a weak antagonist of the α_{1A}-adrenoceptor, dopamine D_1 receptor, and 5-HT2B receptor. In addition, dapoxetine also has a weak, but uncharacterized, affinity for histamine type 1 and 2 receptors, in addition to voltage-sensitive Ca^{2+} channels and Na^{+} channels. Thus, it would be reasonable to suggest that the efficacy of dapoxetine in delaying ejaculation is not accounted for by the pharmacological properties of the drug. By contrast, the rapid absorption of the drug might lead to an abrupt increase in extracellular 5-HT after administration that might be sufficient to overwhelm the compensating autoregulation processes. Does the mechanism of action of short-acting SSRIs differ from that of the conventional crSSRI mechanism of action? Either such agents do not cause the autoreceptor activation and compensation reported using crSSRIs or these effects occur, but they simply cannot prevent the action of short-acting SSRIs (Giuliano, 2007a). Monoamine autoreceptors are typically activated within milliseconds of neurotransmitter release (Davidson and Stamford, 1995); therefore, autoreceptor compensation should be a good temporal match for the elevated perisynaptic level of 5-HT caused by a short-acting SSRI. It is unlikely that the effect of the short-acting SSRI could "outrun" autoreceptor activation. It is speculated that autoreceptor activation occurs but has a limited capacity to compensate for the effects of the short-acting SSRI, and the effect of the drug simply exceeds the compensatory capacity of the autoreceptor. Finally, it is possible that short-acting SSRIs have additional effects that contribute to their mechanism of action (Giuliano, 2007a). Fenfluramine, which causes 5-HT release (Fuller et al., 1988), has been reported to delay ejaculation in humans (Cohen and Holbrook, 1999). If short-acting SSRIs had the capacity to directly cause 5-HT release (in a manner similar to that of amphetamine in dopaminergic systems), this would potentially cause an increase in 5-HT-mediated tone that was outside the control of 5-HT1A autoreceptors.

Treatment related side effects with dapoxetine were uncommon and dose-dependent; they included nausea, diarrhea, headache, and dizziness. They were responsible for study discontinuation in 4% (30 mg) and 10% (60 mg) of subjects (Porst et al., 2010). According to ISSM, there is level 1a evidence to support the efficacy and safety of on-demand dosing of dapoxetine for the treatment of lifelong and acquired PE (Althof et al., 2010; Table 2).

3. On-Demand Antidepressant Selective Serotonin-Reuptake Inhibitors and Clomipramine. Patients are often reluctant to take psychoactive drugs over a long period of time for a condition that, unlike depression, is transient in its manifestations. Accordingly patients often express the desire to take medication for PE only as needed. This has spawned several trials investigating on-demand dosing using antidepressant SSRIs. In several studies, antidepressant SSRIs were administered on demand 3 to 6 h before anticipated sexual intercourse. The results have been modest. On-demand administration of antidepressant SSRIs resulted in substantially less ejaculatory delay than daily treatment in most studies (McMahon et al., 2004). For instance, in a cohort of 30 patients, paroxetine taken, on average, 5.4 h before intercourse increased the mean IELT by 1.4-fold, from 21 to 36 s (Waldinger et al., 2004). The strongest support for on-demand dosing with SSRIs is derived from protocols that were methodologically less rigorous (McMahon and Touma, 1999).

In three double-blind, placebo-controlled crossover studies (Haensel et al., 1996; Strassberg et al., 1999; Waldinger et al., 2004), on-demand dosing with clomipramine (25 mg, 12–24 h before intercourse) significantly increased the IELT by approximately four times that at baseline in men with PE; however, only the smallest of these trials (Waldinger et al., 2004) used an objective stopwatch technique. Nevertheless, overall, it has been concluded by ISSM that there is level 1a evidence to support the efficacy and safety of off-label on-demand dosing of clomipramine, paroxetine, and sertraline for the treatment of lifelong and acquired PE (Althof et al., 2010; Table 2).

4. Anesthetic Topical Preparations. Application of topical anesthetic to reduce the sensitivity of the glans penis is probably the first pharmacological approach used to treat PE. The principle of action is to reduce sensory inputs during penile stimulation that results in increase of ejaculatory threshold. As early as 1943, Ber-

TABLE 2
Pharmacological treatments for premature ejaculation

IELT is expressed as fold increase compared with placebo. [Adapted from Althof SE, Abdo CH, Dean J, Hackett G, McCabe M, McMahon CG, Rosen RC, Sadovsky R, Waldinger M, Becher E, et al. (2010) International Society for Sexual Medicine's guidelines for the diagnosis and treatment of premature ejaculation. *J Sex Med* **7**:2947–2969. Copyright © 2010 John Wiley & Sons. Used with permission.]

Drug	Regimen	Dose	IELT Increase	Reference	Most Common Side Effects	Status
		mg	*fold*			
Oral						
Dapoxetine	On demand	30–60	2.5–3	Pryor et al., 2006; McMahon et al., 2010	Nausea, headache	Approved in various countries
Paroxetine	Daily	10–40	8	Waldinger et al., 1994	Fatigue, yawning, nausea, diarrhea, decreased libido, erectile dysfunction	Off label
Clomipramine	Daily	12.5–50	6	Goodman, 1980; Althof et al., 1995		Off label
Sertraline	Daily	50–200	5	McMahon, 1998		Off label
Fluoxetine	Daily	20–40	5	Kara et al., 1996		
Citalopram	Daily	20–40	2	Atmaca et al., 2002		Off label
Paroxetine	Daily for 30 days then on demand	10–40	11.6	McMahon and Touma, 1999		Off label
Paroxetine	On demand	10–40	1.4	Waldinger et al., 2004		Off label
Clomipramine	On demand	12.5–50	4	Waldinger et al., 2004		Off label
Topical						
Lidocaine/prilocaine	On demand	2.5%/2.5%	4–6	Busato and Galindo, 2004	Penile numbness, partner genital numbness	Off label

nard Schapiro reported the use of anesthetic ointment to delay ejaculation (Schapiro, 1943). Later, clinical trials have shown the efficacy of two preparations, 1) a eutectic mixture of local anesthetics formulated as a cream made of lidocaine and prilocaine and 2) an extract from Asian natural herbs (Severance Secret cream), in prolonging ejaculation latency up to 6- to 8-fold (Busato and Galindo, 2004; Choi et al., 1999; Table 1). Combination of topical lidocaine and long-term administration of oral fluoxetine (an SSRI) was reported to further improve control of ejaculation compared with fluoxetine alone (Atan et al., 2000). A novel aerosol formulation combining lidocaine and prilocaine, which acts rapidly (5 min compared with 20 to 30 min and 60 min for the above-mentioned creams, respectively) has also been demonstrated effective in delaying ejaculation in PE men (Dinsmore and Wyllie, 2009). Adverse events with creams include penile and vaginal numbness, possibly resulting in anorgasmia in female partner unless a condom is used. Local irritation is the most frequent unwanted effect reported with SS cream that must be washed off the glans penis just before coitus. SS cream has been approved in Korea.

C. Other Treatments

1. Phosphodiesterase Type-5 Inhibitors. Phosphodiesterase type-5 (PDE-5) inhibitors are registered for the treatment of erectile dysfunction. By inhibiting PDE-5, which catabolizes cGMP, in the corpora cavernosa of the penis, these compounds increase relaxation of smooth muscle cells, which is responsible for blood engorgement of corpora cavernosa. The potential of PDE-5 inhibitors for treating PE has been debated. Several clinical trials have been undertaken to evaluate the efficacy of PDE-5 inhibitors in the treatment of PE. However, because of gaps in the design of protocols (small sample size, non-randomized trials), the studies have not provided strong evidence for the efficacy of PDE-5 inhibitors in this indication (Abdel-Hamid et al., 2001; Salonia et al., 2002; Chen et al., 2003). One randomized clinical trial did not evidence lengthening of ejaculation latency (either during sexual intercourse or vibrotactile stimulation) in men treated with sildenafil (McMahon et al., 2005). However, perception of ejaculatory control and overall sexual satisfaction were slightly improved, and the refractory time to achieve a second erection after ejaculation was shortened. Nevertheless, the current level of evidence does not support a significant role of PDE-5 inhibitors in the treatment of PE with the exception of men with acquired PE secondary to comorbid erectile dysfunction (McMahon et al., 2006).

2. Tramadol. Tramadol hydrochloride is a centrally acting opioid analgesic indicated for the treatment of moderate to severe pain. Tramadol is readily absorbed after oral administration and has an elimination half-life of 5 to 7 h. For analgesic purposes, tramadol can be administrated 3 to 4 times a day in tablets of 50 to 100 mg. Side effects reported at doses used for analgesic purposes (up to 400 mg daily) include constipation, sedation, and dry mouth. Tramadol is a mild μ-opioid receptor agonist, but it also displays antagonistic properties on transporter of noradrenaline and 5-HT (Frink et al., 1996). This mechanism of action distinguishes tramadol from other opioids, including morphine. However, in May 2009, the U.S. Food and Drug Administration released a warning letter regarding an addictive potential of tramadol and the possibility of difficulty breathing (U.S. Food and Drug Administration, 2009). One placebo-controlled study reported that tramadol HCl significantly increased IELT compared with placebo (Salem et al., 2008). A larger randomized, double-blind, placebo-controlled, multicenter 12-week study evaluat-

ing the efficacy and safety of two doses of tramadol (62 and 89 mg) by orally disintegrating tablet (ODT) for the treatment of PE was conducted (Bar-Or et al., 2012). A bioequivalence study was previously performed that demonstrated equivalence between tramadol ODT and tramadol HCl. In patients with a history of lifelong PE and an IELT ≤2 min, increases in the median IELT of 0.6 min (1.6-fold), 1.2 min (2.4-fold), and 1.5 min (2.5-fold) have been reported for placebo, 62 mg of tramadol ODT, and 89 mg of tramadol ODT, respectively. It should be noted that there was no dose response-effect with tramadol. The tolerability during the 12-week study period was acceptable for the concerned condition. Overall, tramadol has shown a moderate beneficial effect that seems similar to the efficacy of dapoxetine (Giuliano, 2007b).

From what is known about the neuropharmacology of ejaculation and the mechanism of action of tramadol, the delaying effect on ejaculation could be explained by combined CNS μ-opioid receptor stimulation and increased brain 5-HT availability. However, the beneficial effect of tramadol in PE is yet not supported by a high level of evidence. In addition, efficacy and tolerability of tramadol would have to be further confirmed in more patients and over longer term. Because tramadol HCl is widely available as a generic drug for the treatment of pain, it would be advisable to also assess its efficacy as an on demand treatment in PE in larger trials. Tramadol HCl is expected to be effective (Salem et al., 2008) and would become an opportunity for men complaining about PE, especially in the countries in which dapoxetine is not available.

3. α_1-Adrenoreceptor Antagonists. Treatment of hypertension with peripherally acting sympatholytics (e.g., phenoxybenzamine and guanidine derivatives) has been repeatedly reported to cause ejaculatory failure or retrograde ejaculation. Selective antagonists for α_1-adrenoreceptors (more particularly α_{1A} subtypes, which are predominantly expressed in the urogenital tract) are the standard of care for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia. Alfuzosin and tamsulosin are the most widely prescribed drugs for this indication. It has been claimed that these compounds are uroselective. The incidence of ejaculatory disorders varies from less than 1% (alfuzosin) to 4 to 18% (tamsulosin) (Rosen et al., 2005). Evidence has been provided that tamsulosin dose-dependently reduces the volume of expelled sperm, the underlying mechanism being loss of seminal emission (Hellstrom et al., 2005; Hisasue et al., 2006). Blockade of α_{1A}-adrenoreceptors expressed in seminal vesicles and vas deferens may be responsible for tamsulosin side effect on ejaculation (Hisasue et al., 2006). A central effect is also plausible, because tamsulosin shows affinity for D_2-like and 5-HT1A receptors, which play a key role in brain control of ejaculation (Giuliano, 2006).

Only a few clinical studies have been designed to assess the potential of α_1-adrenoreceptor antagonists in PE (Beretta et al., 1986; Cavallini, 1995; Başar et al., 2005). PE symptoms were improved in 50 to 67% of the subjects. However, adequately powered placebo-controlled clinical trials with objective measures (IELT) are lacking to support the role for α_1-adrenoreceptor blockers in the treatment of PE.

D. Potential Future Pharmacological Treatments of Premature Ejaculation

1. Dopamine Receptor Antagonists. All currently used antipsychotic drugs display adverse effects of various types on sexual function and more particularly on libido (for review, see Stimmel and Gutierrez, 2006). Several case reports have evidenced anejaculation in patients suffering from schizophrenia treated with either conventional or atypical antipsychotics (Jeffries et al., 1996; Raja, 1999). In a preliminary double-blinded placebo-controlled clinical trial in a cohort of 49 men with PE, the antipsychotic levosulpiride was reported to substantially increase (>+200%) ejaculation latency in 76% of the subjects 2 months after treatment initiation (Greco et al., 2002). Antipsychotics block dopamine receptors (essentially D_2-like subtype receptors) but some of them (e.g., chlorpromazine, clozapine, and risperidone) also interact with 5-HT2A receptors. Inhibition of dopamine transmission through interaction with D_2-like receptors in incertohypothalamic and mesolimbic pathways explains the wide range of sexual dysfunctions reported with these agents (Stimmel and Gutierrez, 2006). This compromises their use for the treatment of PE. However, evidence gathered in rats that selective blockade of the D_3 receptor subtype specifically affects ejaculatory process without altering other aspects of the male sexual response (Clément et al., 2009b) should open clinical perspectives.

2. GABA Receptor Agonists. The use of benzodiazepine anxiolytics, which enhance GABAergic transmission, for relieving PE has been suggested (Hughes, 1964; Segraves, 1987; Metz and Pryor, 2000), although evidence-based medicine data are lacking. Because of the side-effect profile of GABA full agonists, partial agonists were developed and found to be better tolerated. It was observed, during a phase II trial involving persons subject to stuttering, that pagoclone (GABA-A partial agonist) had sexual side effects. A phase II trial for pagoclone in PE was then undertaken (trial NTC00370981; http://www.clinicaltrials.gov) but an interim analysis (released in September 2006) revealed only a slight effect at the highest dose. Clinical development of this molecule for PE was thus discontinued. However, based on the observation of the effect of intrathecal baclofen on ejaculation in patients with spinal cord injuries (Denys et al., 1998), it can be suggested that selective targeting of GABA-B receptor subtypes with partial agonist might have potential for treating PE.

3. Neurokinin-1 Receptor Antagonists. In view of the pivotal position NK1 receptors occupy in the spinal ejaculatory network and preliminary pharmacological results in laboratory animals (Truitt and Coolen, 2002; Xu et al., 2006; Clement et al., 2009a), blocking those receptors might represent a potential approach for delaying ejaculation in patients with PE. A main issue to be addressed beforehand is the occurrence of NK1 receptors in the key component of the spinal circuitry of ejaculation in human. Careful examination of ejaculatory dysfunctions in patients with spinal cord injuries (Grossiord et al., 1978; Brindley, 1981; Beretta et al., 1989) provides arguments in favor of the existence of a SGE in man, located in the midlumbar spinal segments. However, neurochemical characterization of the human SGE, and more particularly detection of NK1 receptors, remains to be performed. As for OT receptor ligands, the synthesis of nonpeptide NK1 receptor antagonists reaching CNS is of particular importance. Such antagonists are currently evaluated in phase II clinical trials for conditions other than PE (post-traumatic stress disorders, depression, anxiety, etc.).

4. Oxytocin Receptor Antagonists. The large spectrum of sexual functions (i.e., erection, libido, arousal) involving OT is to be considered for the treatment of PE. Better delineating the various intracellular signaling pathways modulated by OT receptors might provide solution for specifically managing PE. The notion of OT receptor "agonists" and "antagonists" becomes vague when regarding the coupling of OT receptors to different G proteins. All OT receptors ligands have the putative potential to stimulate dual signaling responses in neurons expressing those receptors. Moreover, targeting CNS OT receptors is necessary for PE treatment. This issue has been tackled by developing non–peptide-selective ligands that are capable of crossing the blood-brain barrier in sufficient quantity after oral administration. One representative example of these compounds (epelsiban; GSK557296) is under current investigation in men with PE (phase II; trial NCT01021553, http://www.clinicaltrials.gov). If OT ligands are efficient in delaying ejaculation in patients with PE, as expected, the diversity of pathways modulated by OT receptors and the different levels of action of CNS-penetrating OT receptor ligands may complicate the understanding of their exact mechanism of action.

5. Purinergic 2 Receptor Antagonists. The results of in vitro study of human tissues suggest an important role of P2X1/2 receptors in the emission phase of ejaculation (Banks et al., 2006). However, because of the paucity of experimental data in integrated models, the physiological significance of P2X1/2 receptors function in ejaculation is still poorly understood. Moreover, study of the P2X1/2 receptors continues to be hampered by the lack of potent and selective antagonists, although recent progress in this field could lead to interesting perspectives. Assessing the action of such P2X1/2-selective antagonists in animal models of ejaculation is necessary before opening new therapeutic avenues. Nevertheless, on the basis of the observation that deleting the *P2X1* gene in male mice results in a decrease in reproductive capacity (Mulryan et al., 2000), the risk of infertility should be cautiously addressed before the clinical development of P2X1/2 receptors blockers.

6. Serotonin 1A Receptor Antagonists. On the basis of the animal findings supporting a considerable role for 5-HT1A receptors in the control of the ejaculatory response (see section III.C.5.), targeting this receptor subtype with a selective antagonist may be a relevant pharmacological strategy for treating PE. Blockade of 5-HT1A receptors in copulating rats was not found to modify ejaculatory behavior (Ahlenius and Larsson, 1998; de Jong et al., 2005). However, combination of 5-HT1A antagonist with 5-HT synthesis precursor (Ahlenius and Larsson, 1998) or short-term SSRI administration (Looney et al., 2005; de Jong et al., 2005) led to a marked lengthening of ejaculation latency. It can be inferred that 5-HT1A receptors intervene in the ejaculatory response when 5-HT levels become elevated and that concomitant inhibition of 5-HT1A receptors and increase in brain 5-HT levels prevent occurrence of ejaculation. Synthesis of pharmacological compounds exhibiting combined activities on 5-HT1A receptors (antagonism or partial agonism) and 5-HT transporters (inhibitor) has been described previously (Dawson and Bromidge, 2008). However, as far as we know, action of such a dual activity compound on ejaculatory response is not documented.

V. Conclusions

The crucial role of CNS and a specifically dedicated network in ejaculation is becoming well documented, although numerous gaps are to be filled in to further improve our understanding of the neurobiology of ejaculation. More particularly, it is still not clearly established that the spinal generator for ejaculation described in the male rat exists in humans. The neurochemical control of ejaculation is highly complex because of the variety of neurotransmitters/neuromodulators and receptors involved at multiple levels of the nervous system. Nevertheless, recent advances in this field led to the identification of pharmacological targets that can be manipulated to modulate the ejaculatory response. More interestingly, it was found to be feasible in laboratory animals to specifically affect the ejaculatory process without altering other aspects of the male sexual response. Pursuing basic research that aims at clarifying the specific mechanisms controlling ejaculation will undoubtedly help to open new avenues for the pharmacological treatment of PE. Clinical trials carried out to date have shown, at best, moderately effective strategies that alleviate PE in men. Moreover, oral medicines currently available are not devoid of unwanted side effects

that can compromise their use. It can thus be concluded that there is definitely room for progress in the pharmacological management of PE.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Giuliano and Clément.

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